# Administering Bolus Intravenous Norepinephrine to Improve the Peripheral Arterial Line Cannulation: Randomized Controlled Trial

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## Abstract

**Background:** The conventional arterial line insertion may pose challenges in some cases. The methods to enhance the success rate of arterial line cannulation require specific equipment and skill, in contrast to the conventional palpation technique.

**Objective:** To investigate whether administering intravenous norepinephrine as a bolus dose can increase the success rate of arterial line insertion using the conventional technique.

**Materials and Methods:** The randomized study included adults undergoing elective surgery and requiring the perioperative arterial line insertion. The participants were allocated into two groups: the experimental norepinephrine group (NE group) received five mcg of norepinephrine intravenously, and the control group (NSS group) received an intravenous saline solution before inserting the arterial line. The primary outcome was the difference in the number of puncture attempts. The secondary outcomes included the total time to successful arterial cannulation and complications related to the procedure.

**Results:** Ninety-two patients were randomized and analyzed, with 46 in the NE group and 46 in the NSS group. There was a significantly lower in the number of arterial puncture attempts in the NE group than the NSS group (p=0.034), demonstrating a notably higher first-attempt success rate [29 (63%) vs. 25 (54.3%)] and fewer patients required more than two attempts [3 (6.5%) vs. 12 (26.1%)]. The time to successful arterial line cannulation was significantly lower in the NE group compared to the NSS group [124 (59-227) seconds vs. 184 (92-480) seconds, p=0.028]. Furthermore, the results also demonstrated a significantly lower incidence of complications in the NE group compared to the NSS group [8 (17.4%) vs. 20 (43.5%), RR 0.400, 95% CI 0.197 to 0.814, p=0.007].

**Conclusion:** Intravenous norepinephrine administration before the conventional arterial line insertion can reduce the number of attempts required, decrease total time to success, and lower the incidence of complications related to the arterial line insertion.

**Keywords:** Arterial line; Arterial line insertion; Arterial line cannulation; Norepinephrine

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The arterial line insertion is indicated in patients needing continuous hemodynamic monitoring or frequent blood sampling. The conventional arterial line insertion uses the palpation technique, in which the performer palpates the arterial pulse to identify the anatomical landmark and inserts the line. This technique may present challenges, particularly in patients with hypotension, peripheral arterial disease, or other conditions hindering the palpation of arterial pulses[1,2]. Suppose the physician encounters difficulty during the first attempt at arterial line cannulation. In that case, the subsequent attempts may delay the care and increase the likelihood of complications such as hematoma, distal ischemia, intra-arterial thrombosis, puncture site infection, and nerve injury[1,3].

**What is already known about this topic?**

Intravenous norepinephrine administration increases blood pressure and enhances peripheral pulse pressure.

**What does this study add?**

Intravenous norepinephrine administration as a bolus dose facilitates more distinct pulse palpation, which can enhance the successful arterial line cannulation without an increase in the complication rate.

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Other alternative methods to enhance the success rate of arterial line cannulation include using a Doppler-assisted technique to identify where the artery is or using an ultrasound-guided technique to visualize the artery at the time of line insertion[2]. This technique reduces the number of attempts and decreases the time to success without increasing the risk of complications associated with arterial line insertion[2,4-10]. However, the ultrasound machine is not always available in every operating room and requires expertise for ultrasound-guided arterial line insertion.

Norepinephrine is a sympathomimetic drug that activates alpha- and beta-adrenergic receptors, resulting in increased peripheral vascular resistance and systemic blood pressure. The onset of intravenous norepinephrine is less than 2 minutes, and the duration of action is 1-2 minutes.

Our trial question is whether administering norepinephrine as a bolus dose via the peripheral vein before arterial line insertion using the conventional technique can increase the success rate. The other outcomes include the total time to succeed in arterial line cannulation and the incidence of complications associated with arterial line cannulation. We hypothesized that administering norepinephrine intravenously would enhance peripheral pulse pressure and facilitate more distinct pulse palpation. Norepinephrine administration could increase the success rate of radial arterial cannulation, decrease the total time to success, and minimize the number of puncture attempts.

## Materials and Methods

### Study Design

The study design adhered to the CONSORT guidelines and the Declaration of Helsinki. This prospective, randomized, placebo-controlled trial involved 92 patients at Ramathibodi Hospital between January 2023 and January 2024. The study was endorsed by the Ramathibodi Ethics Committee (MURA2022/526, Date of approval: September 14, 2022) and registered at the Thai Clinical Trials Registry (TCTR20221210001, Date of registration: December 10, 2022). The researchers informed all enrolled patients about the research methods and provided written informed consent. The first patient was recruited for the study on January 10, 2023.

### Patients

Adult patients aged 18 to 70 years with American Society of Anesthesiologists (ASA) physical status I to III scheduled for elective surgery under general anesthesia and requiring arterial line insertion were considered for potential enrollment. The research team informed each patient of the details and provided written informed consent. Exclusion criteria included patients who refused or requested to withdraw from the study, patients undergoing emergent surgery, pregnant or lactating patients, severe obesity patients (body mass index (BMI) $\geq$35 kg.m$^{-2}$), patients with a history of allergy to norepinephrine (including sodium metabisulfite or sulfa derivatives), patients with uncontrolled hypertension (defined as baseline systolic blood pressure greater than 160 mmHg), patients with uncontrolled systemic disease (such as hyperthyroidism or pheochromocytoma), and patients with vascular disease (such as peripheral artery disease, vascular aneurysm, or mesenteric ischemia). The patients who received continuous vasopressor or inotropic drug administration before arterial line insertion or were currently taking monoamine oxidase inhibitors or tricyclic antidepressants would be excluded from the study.

### Randomization, Intervention, and Blinding

The researchers used a computer-generated block of 4 randomization and allocated 92 patients into two groups, 46 for each group. The experimental group (NE group) received five mcg of norepinephrine intravenously before inserting the arterial line. The control group (NSS group) received an intravenous saline solution as a placebo before the arterial line insertion. The groups were concealed and randomized using opaque envelopes to ensure that neither the patients, the anesthesiologist staff, the performers, nor the nurse anesthetist was aware of the group allocation. Each group was masked by one of the researchers who prepared the intervention using an identical 5-mL syringe. The syringe contained either five mcg of norepinephrine or normal saline solution with a total volume of up to 5 mL without labeling. The performer was designated to the trainee within the anesthetic residency program who had experience in perioperative care for more than six months.

The participant's hand was supinated and slightly extended using a roll under the wrist, which was stabilized by taping to the armboard. The skin was disinfected using chlorhexidine with alcohol before the induction of general anesthesia, along with the insertion of an endotracheal tube. The medication used to induce anesthesia depends on the discretion of the anesthesiologist who was responsible for the patient. One minute after the endotracheal tube was intubated, the nurse anesthetist would administer

either five mcg of norepinephrine or a placebo within a 5-mL syringe specified to each group and then administer 10 mL of normal saline via peripheral venous line. One minute after the intervention drug was injected, the blood pressure was recorded, and the performer started palpating the pulse at the radial artery with a non-dominant hand and performed the arterial line insertion using a 20-G intravenous catheter. The performer was not allowed to use a guidewire to assist catheter advancement. After the successful arterial line insertion, the arterial blood pressure would be transduced to show the arterial waveform. During the arterial line cannulation, the vital signs (including blood pressure, heart rate, and arterial saturation) were concealed from the performer but were monitored by the anesthesiologist staff. The performer was allowed a maximum of four attempts in case of unsuccessful cannulation. If there was still an inability to complete the arterial line insertion after four attempts, more experienced personnel would be tasked with completing it.

The patient demographic data, hemodynamic parameters, time to successful arterial cannulation, number of attempts, and number of complications were collected by the nurse anesthetist, who was also blinded to the intervention and not involved in the study outcome. The hemodynamic data included baseline blood pressure, blood pressure one minute after intubation, blood pressure one minute after the intervention, and blood pressure after successful arterial line cannulation.

In terms of safety, administering five mcg of norepinephrine after intubation might increase blood pressure higher than expected. If immediately after intubation the patient's systolic blood pressure was more than 160 mmHg, they were considered to have dropped out of the study and treated with an appropriate antihypertensive medication to normalize their blood pressure.

### Outcome

The primary outcome was the difference in the number of attempts required to achieve success, measured as the number of skin punctures needed to successfully insert an arterial catheter. The secondary outcomes included time to success, defined as the time from the performer's finger contacting the participant's skin to palpate the peripheral pulse until the display of an arterial waveform appeared on the monitor, and the number of complications, such as puncture-site hematoma or distal ischemia. The distal ischemia was identified when the distal part of the inserted area appeared pale, and the capillary refill was over 3 seconds. If distal ischemia was observed, a vascular surgeon consultation was considered.

### Statistical Analysis

The sample size was determined from Ueda et al.'s study[2], which reported that the first-attempt success rate for arterial line cannulation by palpation was 39%. We hypothesized that administering five mcg of norepinephrine intravenously before attempting insertion would increase the first attempt success of arterial line cannulation by conventional technique to 70%. The total sample size was 92 patients, 46 patients in each group, with a type I error (α) of 0.05, a type II error (β) of 20%, and assuming a 1:1 ratio of positive and negative assessment results among patients.

This statistical analysis used an intention-to-treat approach, performed in Stata Statistical Software, version 18 (StataCorp LLC, College Station, TX, USA). The categorical variables were reported in numbers and percentages. The continuous variables were tested with a Shapiro-Wilk test. The normally distributed continuous variables were reported in the mean and standard deviation, and the non-normally distributed variables were reported in the median and interquartile range (IQR).

To compare the differences between the two groups, the chi-square and Monte Carlo tests were used for categorical data, the independent t-test was used for parametrically distributed continuous data, and the Mann-Whitney U test was employed if the data were non-parametric. A generalized estimating equation (GEE) analysis with a Gaussian family and identity link was used to examine the effect of group and time on repeated measurement, accounting for within-subject correlation using an exchangeable working correlation structure. A p-value less than 0.05 was considered statistically significant.

## Results

Ninety-two participants were enrolled and randomized into 46 patients in the NE group and 46 in the NSS group. Table 1 shows no significant differences between the two groups in baseline characteristics, including age, BMI, sex, ASA physical status, and level of performer. A flowchart of the study's progression is shown in Figure 1.

There was a significant difference in the number of puncture attempts between the two groups (p=0.034). The patients in the NE group required fewer puncture attempts than the NSS group, demonstrated a notably higher first-attempt success rate [29 (63%) vs. 25

**Table 1.** Patient's demographic data and level of performer

| Parameter | NE group (n=46) | NSS group (n=46) | p-value |
|---|---|---|---|
| Age (years); mean±SD | 58.91±10.97 | 57.76±11.11 | 0.618 |
| Body mass index (kg.m$^{-2}$); mean±SD | 24.32±4.17 | 25.17±4.13 | 0.331 |
| Sex; n (%) | | | 0.675 |
| Male | 22 (47.8) | 20 (43.5) | |
| Female | 24 (52.2) | 26 (56.5) | |
| ASA physical status; n (%) | | | 0.455 |
| I | 1 (2.2) | 0 (0.0) | |
| II | 18 (39.1) | 22 (47.8) | |
| III | 27 (58.7) | 24 (52.2) | |
| Level of performer; n (%) | | | 0.186 |
| First-year resident | 22 (47.8) | 15 (32.6) | |
| Second-year resident | 12 (26.1) | 20 (43.5) | |
| Third-year resident | 12 (26.1) | 11 (23.9) | |

ASA=American Society of Anesthesiologists; NE=norepinephrine group; NSS=normal saline; SD=standard deviation

**Table 2.** Comparison of outcomes between two groups

| Parameter | NE group (n=46) | NSS group (n=46) | p-value |
|---|---|---|---|
| Number of attempts; n (%) | | | 0.034* |
| 1 | 29 (63.0) | 25 (54.3) | |
| 2 | 14 (30.4) | 9 (19.6) | |
| More than 2 | 3 (6.5) | 12 (26.1) | |
| Time to success (seconds); median (IQR) | 124 (59-227) | 184 (92-480) | 0.028* |
| Complication; n (%) | | | |
| Hematoma | 8 (17.4) | 20 (43.5) | 0.007* |

NE=norepinephrine group; NSS=normal saline; IQR=interquartile range
* Statistically significant

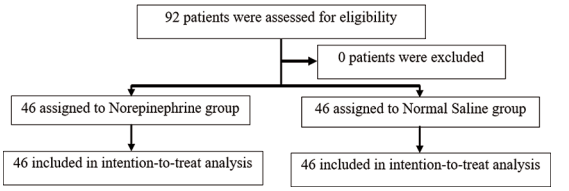


**Figure 1.** Flow chart of the study's progression.

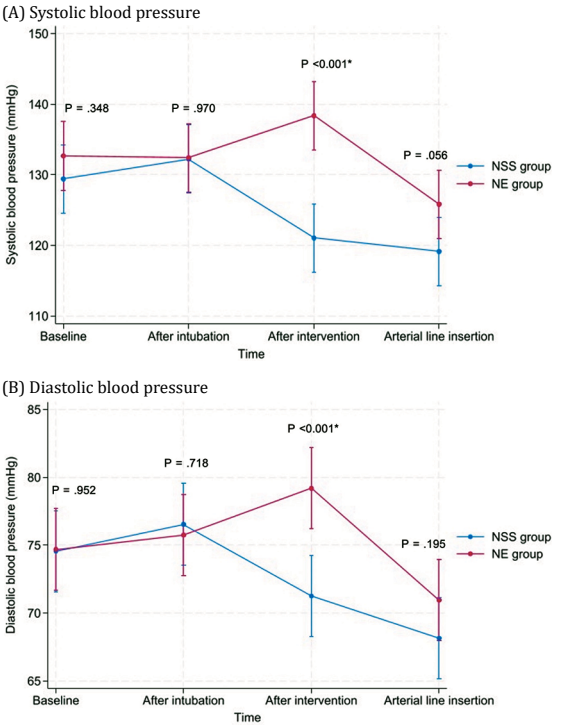


**Figure 2.** Comparison of hemodynamic parameters between two groups at four period of time using generalized estimating equation (GEE) analysis.

DBP, diastolic blood pressure; NE, norepinephrine group; NSS, normal saline; SBP, systolic blood pressure
Data are presented as means and 95% confidence interval.
* Statistically significant

(54.3%)], and fewer patients required more than two attempts [3 (6.5%) vs. 12 (26.1%)], as shown in Table 2.

The time to successful arterial line cannulation was significantly lower in the NE group compared to the NSS group [124 (IQR 59-227) seconds vs. 184 (IQR 92-480) seconds, p=0.028). Furthermore, patients in the NE group had a significantly lower incidence of complications compared to the NSS group [8 (17.4%) vs. 20 (43.5%), RR 0.400, 95% CI 0.197 to 0.814, p=0.007). All the complications were hematoma at the puncture site, and no cases were diagnosed with distal ischemia, as illustrated in Table 2.

After using GEE to analyze hemodynamic data, the NE group showed significantly higher systolic and diastolic blood pressure at one minute after intervention than the NSS group. The mean difference in systolic blood pressure was 17.3 mmHg (95% CI 10.44 to 24.17, p<0.001), and diastolic blood pressure was 7.93 mmHg (95% CI 3.69 to 12.17, p<0.001). The other parameters were insignificant, as shown in Figure 2. This could be explained by a bolus dose of norepinephrine to increase blood pressure (both systolic and diastolic) for only a short time during arterial line puncture. In our trial, no patients had systolic blood pressure greater than 160 mmHg immediately after intubation. Four patients in the NE group had systolic blood pressure above 160 mmHg at 1 minute after norepinephrine administration (170, 164, 161, and 163 mmHg); none had serious complications.

## Discussion

This randomized, placebo-controlled trial found

that intravenous norepinephrine administration before arterial line cannulation improved the success rate using the conventional radial arterial line cannulation. This could be explained by the mechanism of norepinephrine, which increases systemic vascular resistance by activating alpha-1 and beta-1 adrenergic receptors to increase cardiac output and intraluminal pressure within the artery, making it much easier for the operator to identify the arterial pulse. The radial artery was chosen for its superficial course, dual blood supply to the hand, and low risk of complications. The NE group had a lower proportion of patients who required more than 2 attempts at arterial line insertion and a significantly shorter time to success than the NSS group. This could be explained by the effect of norepinephrine, which showed a significantly higher systolic blood pressure one minute after drug administration, when the performer began palpating the radial artery pulse. Regarding complications, the NE group had a lower incidence of hematoma at the puncture site. This might be explained by the decreased number of arterial puncture attempts and the vasoconstriction effect of norepinephrine, which attenuates vascular bleeding.

We selected intravenous norepinephrine administration as an alternative to improve arterial line insertion using the conventional technique rather than the ultrasound-guided technique, since the ultrasound machine may not always be available. Norepinephrine had a rapid onset and short duration and was available in all the operating rooms. We calculated the dose of norepinephrine from Allwood et al.'s study[11], which showed that 10 micrograms per minute might increase systolic blood pressure by about 50 mmHg. We decided to use five mcg of norepinephrine to avoid an excessive increase in blood pressure. Conventional arterial line insertion may be broadly applicable because the palpation of the arterial pulse is a general skill that all physicians can perform, so our result could apply to any conventional arterial line cannulation without the limitation of an unavailable ultrasound machine, and may be helpful in specific cases, such as hypotensive patients, to assess their hemodynamic data earlier than the ultrasound-guided technique.

Our trial aimed to evaluate the benefits of intravenous norepinephrine in improving the success of arterial line insertion, with patient safety as a primary concern. This dosage was deemed safe and appropriate for the study's objective. The protocol established the exclusion criteria for patients who may be at risk from norepinephrine. Additionally, if enrolled patients had systolic blood pressure greater than 160 mmHg one minute after intubation, they would be dropped from the study and treated with antihypertensive medication to ensure their safety.

A limitation of our study was that we did not assign a specific induction protocol, including the induction agent and dosage, which could have affected the patient's hemodynamics during arterial line insertion. Each patient was different, so we assigned the responsible anesthesiologist to decide which induction agent to use. However, there was no significant difference in blood pressure between the two groups one minute after intubation.

The other limitation was that we did not use ultrasound to measure the diameter of the radial artery or to assess how norepinephrine affects the vessel. The reason was that the bolus dose of norepinephrine increased blood pressure rapidly and only for a short time. If we used the ultrasound to measure the vessel, there might be a decrease in the change as the norepinephrine's action declines. Our trial only aims to assess the success rate of arterial line insertion. Using norepinephrine to assist in specific patient groups, such as hypotensive patients, and the change in vessel diameter due to norepinephrine requires further investigation.

## Conclusion

Intravenous norepinephrine administration before the conventional arterial line insertion enhances the success rate and reduces the number of attempts. This approach may decrease time to success and reduce complications associated with arterial line insertion.

## Authors Contributions

NP contributed to the study design, data collection, article drafting, and approval of the published version. SM contributed to the study design, data interpretation, and manuscript revision. WR contributed to data collection, analysis, and manuscript revision. NK contributed to the study design, data collection, analysis, manuscript revision, and approval of the version to be published. All authors have read and approved the manuscript.

## Clinical Trial Registration

The study was registered at the Thai Clinical Trials Registry (TCTR20221210001, Principal investigator: NP, Date of registration: December 10, 2022).

## Conflicts of Interest

The authors declare no conflict of interests.

## Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

The study was approved by the Ramathibodi Ethics Committee (MURA2022/526, Date of approval: September 14, 2022). The researchers informed all enrolled patients about the research methods and provided written informed consent. The first patient was enrolled in the study on January 10, 2023.

## Funding Disclosure

This research project had no funding support.

## Use of Artificial Intelligence

The authors utilized Grammarly to refine the language and clarity of this manuscript. All AI-generated suggestions were reviewed and edited by the authors, who maintain full responsibility for the final content and its accuracy.

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